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Evaluation and Management of Antimicrobial Resistance

Introduction

Antibiotic-resistant bacteria, such as vancomycin-resistant enterococci (VRE) and organisms with extended spectrum beta-lactamases (ESBL), have become an ever-increasing problem, particularly among hospitalized patients. Resistance to antibacterials has been observed since their introduction, but recently "super-resistant" bacteria have been reported that leave only one antibacterial choice for treatment.

The prevalence of the different types of resistant bacteria has increased at varying rates. Oxacillin-resistant *Staphylococcus aureus* (ORSA), a clinically isolated pathogen since the early 1960s, has increased among U.S. hospitals from 2.4% in 1975 to 29% in 1991. Penicillin-resistant pneumococci, First reported in 1967, have increased worldwide, with some areas of the U.S. reporting very high rates of resistance among clinical isolates. Gram-negative bacilli, primarily *Klebsiella pneumoniae* and *Escherichia coli*, that carry transferable resistance to extended-spectrum beta-lactams, have also become more common, with one U.S. study reporting up to 8.6% of clinical isolates having at least intermediate resistance to ceftazidime. Although vancomycin has been used for more than 30 years, resistance to this drug has only recently emerged. The prevalence of VRE in the U.S. has increased among nosocomial isolates from less than 0.5% in 1989 to more than 10% in 1995, a 20-fold increase. A variety of patient factors have been associated with the development of resistance (Table 1).

The increasing prevalence of resistant bacteria reported nationally has also been observed at the Clinical Center in the past few years, although the presence of these organisms is relatively rare compared to most community hospitals (see Table 2 for a list of resistant bacteria commonly encountered at U.S. hospitals). The most common clinically relevant resistant organism cultured at this institution has been ORSA. Since 1984 there have been a total of 94 patients who have had at least one ORSA-positive culture. The number of patients with this organism has remained fairly constant between

1984 and 1996, with the identification of an average of six new patients each year. There have been only eight patients with VRE identified at the Clinical Center since 1994. There have also been five patients who have had an ESBL-producing organism cultured from a clinical specimen, all in 1996.

Table 1. Factors Associated with the Development of Bacterial Resistance

Site of Infection	**Inappropriate use of antimicrobials**
Bone Lower respiratory tract Central nervous system	Suboptimal dosing or duration Chronic or repeated administration Improper antibiotic selection (e.g., overuse of broad-spectrum agents)
Underlying condition of host	**Other**
Immune system compromise Cystic fibrosis Central nervous system	Intensive care unit setting Mechanical ventilation Presence of mechanical or other foreign material

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Beta-Lactamase-Producing Gram-Negative Bacilli

Beta-lactamases are the most common single cause of bacterial resistance to beta-lactam antibiotics. Numerous chromosomal and plasmid-mediated types are known. These enzymes can hydrolyze the beta-lactam ring of penicillins, cephalosporins, and related antimicrobial drugs, rendering them inactive.

Various cephalosporins are susceptible to cleavage by a variety of beta-lactamases commonly found in gram-negative bacilli, including the chromosomal beta-lactamases of *Entero-bacter* and *Pseudomonas* as well as the common plasmid-borne enzymes of the Enterobacteriaceae. The plasmid-mediated enzymes have become common in staphylococci, enteric gram-negative bacilli, *Haemophilus influenzae*, and *Neisseria gonorrheae*.

The most common beta-lactamase in enterobacteria is the plasmid-mediated TEM-1 enzyme, which is responsible for most of the ampicillin resistance seen in *E. coli* isolates. Other common types are TEM-2 and SHV enzymes. Unlike the chromosomal types, the plasmid-mediated types are usually inactivated by beta-lactamase inhibitors such as clavulanic acid.

Enteric gram-negative bacilli producing extended-spectrum beta-lactamases were first described in Germany in 1983. They are transferable plasmid-mediated enzymes. The most notable feature of these enzymes is their ability to attack extended spectrum cephalosporins (e.g., ceftazidime, cefotaxime, and ceftriaxone) as well as monobactams such as aztreonam. They also attack narrow spectrum cephalosporins (e.g., cephalothin) and anti-gram-negative penicillins (e.g., piperacillin). Cephamycins such as cefoxitin and carbapenems such as imipenem are stable. The majority of the ESBL enzymes reflect the above pattern of activity, but individual enzymes vary in the level of resistance they cause to different compounds. Resistance to ceftazidime and aztreonam, and susceptibility to cephamycins are useful markers of ESBL production in gram-negative bacilli. The most common ESBL-producing strains are *Klebsiella pneumoniae*, other *Klebsiella* species, and *E. coli*.

Oxacillin-Resistant Staphylococcus Aureus (ORSA)

Oxacillin-resistant *Staphylococcus aureus* (also known as methicillin-resistant *Staphylococcus aureus*) has become a major noscomial pathogen in community, long-term care, and tertiary care hospitals. This pathogen can cause serious infection, and contributes signiÞcantly to mortality and morbidity in hospitals worldwide.

Resistance to oxacillin and methicillin in staphylococci is mediated by alterations in membrane-bound enzymes called penicillin binding proteins (PBPs). PBPs perform important functions for cell survival and are the targets for beta-lactam antibiotics. There must be a high afÞnity between the drug and the bacterial PBPs for the antibiotic to be effective. In the typical oxacilllin-resistant strain of *S. aureus*, the drug resistant target termed PBP2a (or PBP2') mediates clinically relevant resistance to all beta-lactam antibiotics. PBP2a is a unique cell wall-synthesizing enzyme that confers resistance ranging from a few organisms to a majority of organisms in a population. The low afÞnity of PBP2a for beta-lactams enables the organism to survive in the presence of otherwise lethal concentrations of beta-lactam antibiotics. PBP2a is encoded by the chromosomal gene *mec*A which is highly conserved in clinical isolates of oxacillin-resistant staphylococci.

ORSA isolates are frequently resistant to a wide range of antibiotics by a variety of different resistance mechanisms (e.g., many isolates are resistant to aminoglycosides due to the presence of aminoglycoside modifying enzymes).

Vancomycin-Resistant Enterococci (VRE) and Aminoglycoside-Resistant

Enterococci

Enterococci are currently a major cause of nosocomial infection, and antibiotic resistance in these organims has become a particular problem in hospitals.

Enterococci have intrinsic resistance to a wide variety of antimicrobial agents. They also have the ability to acquire resistance by mutation or by receipt of foreign genetic material through the transfer of plasmids and transposons. Until recently, vancomycin was the only drug that could be consistently relied upon to treat multidrug resistant enterococci.

Vancomycin-resistant enterococci were Þrst reported in Europe in the mid 1980s and later in the U.S. The most frequent enterococcal species demonstrating acquired resistance to glycopeptides are *E. faecium* and *E. faecalis*. Acquired vancomycin resistance in enterococci is mediated by complex mechanisms encoding an alternative pathway for the production of a modiÞed cell wall component with markedly reduced afÞnity for vancomycin. Glycopeptide-resistant enterococci are divided into different phenotypes primarily on the basis of their resistance to vancomycin and teicoplanin. Four phenotypes have been described, namely Van A, Van B, Van C, and Van D. VanA is the most common phenotype, and is manifested by high-level resistance to vancomycin, and moderate or high level resistance to teicoplanin.

Enterococci are also intrinsically resistant to amino-glycosides, but the addition of a beta-lactam antibiotic (e.g., ampicillin) allows entry of the aminoglycoside into the bacterial cell, producing a synergistic combination that results in cell death. Enterococci that are highly resistant to aminoglycosides pose an important clinical problem as these organisms are resistant to synergistic killing by beta-lactam/ aminoglycoside combinations. The resistance is due to the production of plasmid-mediated aminoglycoside-modifying enzymes.

Table 2. Resistant Bacteria Commonly Encountered at U.S. Hospitals

Organism	Mechanism of Resistance	Treatment Options
ESBL[1]-producing gram-negative bacilli	Production of beta-lactamase enzymes which inactivate beta-lactam antibacterial agents	Carbapenems Beta-lactam/beta-lactamase inhibitor combination Fluoroquinolones, aminoglycosides, trimethoprim-sulfamethoxazole
ORSA	Alterations in the penicillin-binding proteins	Vancomycin Teicoplanin

		Mupirocin (topical)
VRE[3]	Modified cell wall precursors with decreased affinity for vancomycin	Teicoplanin Quinupristin-dalfopristin Combinations of beta-lactam or beta-lactams and a glycopeptide

Adopted from Gold HS, Moellering RC. Antimicrobial-drug resistance. N Engl J Med 1996; 335: 1445-53.
[1]*Extended-spectrum beta-lactamase;* [2]*Oxacillin-resistant S. aureus;* [3]*Vancomycin-resistant enterococci*

Management of Patients with Resistant Bacteria at the Clinical Center

Clinical Center patients with a positive culture for a strain of resistant bacteria are immediately placed on isolation precautions that are specific for this situation. These precautions are used to minimize the risk of nosocomial transmission and are based on studies that suggest that spread of these organisms can be limited when a diligent effort is made by healthcare providers. There have been a number of reports of clusters and outbreaks caused by resistant bacteria that have been related to the transient carriage of organisms on healthcare providers' hands as they move from one patient to another. Therefore, glove use and proper handwashing are important mechanisms for decreasing the spread of organisms. Fomites, such as stethoscopes, blood pressure cuffs, and electric thermometers have also been demonstrated to play a role in some outbreaks. Therefore, dedicated equipment is required for patients with positive cultures for resistant bacteria. The environment has also been suggested as a factor in the transmission of resistant organisms, making good housekeeping procedures a necessity.

The precautions currently used at the Clinical Center, called *Resistant Bacteria Precautions*, include: the use of a private room, the use of gloves for all patient contact (masks and gowns may also be needed in special situations), the use of dedicated patient equipment (stethoscope, blood pressure cuff, thermometer, etc.), scrupulous environmental cleaning, the restriction of the patient to his/her assigned room [except for patient-care procedures in ancillary departments and activities approved by Hospital Epidemiology Service (HES)], the restriction of the patient from contact with other patients, and most importantly, the practice of proper handwashing with an antiseptic cleaning agent. These precautions should be initiated as soon as a patient is identiÞed with a resistant organism, and HES should be contacted (496-2209).

Unfortunately, most patients who have been found to be colonized or infected with resistant bacteria will continue to be culture positive as long as they are hospitalized. Attempts at eliminating a resistant organism by treating individuals with different regimens are often unsuccessful,

especially when the site that is positive involves an implanted device, is an unhealed wound, or involves an area that contains large amounts of body secretions (e.g., sputum). Occasionally, patients may be cleared of a resistant organism and can have the special restrictions discontinued. These patients must meet the following criteria: the documentation of two sets of negative cultures obtained 48 hours apart; these cultures must have been collected only after all relevant antibiotics have been discontinued for 24 hours, and must be sent from all previously positive sites.

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